DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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Sidney M. Wolfe, M.D.
Larry D. Sasich, Pharm.D., M.P.H., FASHP
Elizabeth K. Barbehenn, Ph.D.
Public Citizen's Health Research Group
1600 20th Street NW
Washington, DC 20009-1001

Re: Docket No. 99P-2076/CP1

Dear Drs. Wolfe, Sasich, and Barbehenn:

This responds to your citizen petition, dated June 3, 1999, requesting that the Food and Drug Administration (FDA) ban the sale of the drug product trovafloxacin on the United States market. For the reasons discussed below, your citizen petition is denied.

I. Discussion

On December 18, 1997, FDA approved new drug applications for trovafloxacin and alatrofloxacin[1] (brand name Trovan) sponsored by Pfizer Inc. (Pfizer). Trovan is an anti-infective drug product with extended spectrum antibacterial activity. It is the first fluoroquinolone shown to be safe and effective in the treatment of infections caused by the four main categories of bacteria – gram-positive aerobic, gram-negative aerobic, anaerobic, and atypical respiratory pathogens. Trovan was initially approved for treating a broad range of infections, from minor skin infections to severe infections in hospitalized patients. Over 2.5 million prescriptions have been written for Trovan since its launch in February 1998.

After the launch of Trovan, FDA began to receive reports of elevated enzymes and hepatitis in patients after short- and long-term therapy. In July 1998, FDA worked with Pfizer to strengthen Trovan's labeling with respect to potential liver complications. FDA continued to receive reports of liver toxicity, including reports of a more serious nature.

Following discussions with Pfizer, FDA issued a Public Health Advisory (Advisory)(enclosed) on June 9, 1999. As of that date, the Agency had received more than 140 reports of liver complications. Of those reports, 14 represent patients with acute liver failure that the Agency concluded are strongly associated with the drug. Five of those patients required liver transplantation (one subsequently died), five patients died of liver-related disease, and four patients recovered from their acute liver failure without requiring a liver transplant.

The Agency balanced these reports against the potential benefit of using Trovan in the treatment of some serious, life- or limb-threatening infections. Trovan's broad spectrum antibacterial

[1] Trovafloxacin is an oral formulation, and alatrofloxacin is an intravenous formulation.

99P-2076

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activity renders it an important agent for a critically ill patient who is administered antibacterial drugs empirically (where a baseline pathogen is not known) for an infection where various bacterial pathogens may be causative. In a very ill patient, initial narrow spectrum antibacterial therapy may not be prudent and broad spectrum monotherapy may be a particularly desirable feature for a treating physician. Based on these considerations, the Agency concluded that physician's should have access to Trovan under limited circumstances and issued the June Advisory.

In the Advisory, the Agency advised physicians that:

> Trovan should be reserved for use ONLY in the treatment of patients who meet ALL of the following treatment criteria:
>
> - Have at least one of the following infections that is judged by the treating physician to be serious and life- or limb-threatening:
>   - nosocomial pneumonia,
>   - community acquired pneumonia,
>   - complicated intra-abdominal infections (including post-surgical infections),
>   - gynecologic and pelvic infections, or
>   - complicated skin and skin structure infections, including diabetic foot infections;
>
> - Receive their initial therapy in an in-patient health care facility (i.e., hospital or long-term nursing care facility); and
>
> - The treating physician believes that, even given the new safety information, the benefit of the product for the patient outweighs the potential risk. (Advisory at 1)

The Agency further stated that in most cases a patient would begin therapy with intravenous Trovan and could be switched to oral Trovan to complete the entire course if deemed appropriate by the treating physician. Oral therapy may be appropriate initial therapy in some patients with serious and life- or limb-threatening infections, but its use to treat less serious infections is not warranted. FDA also advised that Trovan generally should not be used longer than 14 days and that it should be discontinued prior to 14 days if the patient experiences any clinical signs or symptoms of liver dysfunction (Advisory at 1). FDA worked with Pfizer to make appropriate revisions to the labeling of Trovan.

The Agency and Pfizer have also agreed to a program that will limit the distribution of Trovan to in-patient health care facilities (hospitals and long-term nursing care facilities). In addition, Pfizer is voluntarily recalling Trovan from pharmacies that do not serve in-patient health care facilities.

Finally, with respect to issues you raised regarding the review of the Trovan new drug applications, we note that there were no reports of liver failure, liver transplant, or death due to liver toxicity in the 7,000 patients who were studied in premarketing clinical trials for Trovan. Although there was some evidence of elevated serum transaminases in patients with prostatitis (the only indication requiring more than 14 days of Trovan therapy), the patients did not exhibit clinical symptoms of liver toxicity or experience concomitant increases in serum levels of other liver enzymes. The transaminase abnormalities were observed following discontinuation of the study drug after 28 days of drug therapy. However, these abnormalities slowly resolved during the follow-up/post-therapy period. Because of this evidence, the initial approved Trovan labeling recommended periodic assessment of hepatic function. The Agency continues to believe that approval of the Trovan new drug applications was well supported by the data in the applications.

II. Conclusion

The Agency believes that given the benefits and risks of the drug product, Trovan should be made available only to those patients who may need it for treatment of serious and life- or limb-threatening infections. Limited use and distribution of Trovan is expected to minimize the risks of exposure for other patients. The risk management program described above was designed to achieve this goal. The Agency has determined that implementing the risk management program, revising Trovan's labeling, and restricting Trovan's indications are reasonable and prudent actions at this time. For these reasons, the Agency is denying your request to ban the drug's sale. The Agency will continue to monitor Trovan closely and will take appropriate actions if the evidence with respect to both the benefits and risks of Trovan changes.

Sincerely yours,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

Enclosure